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Children and adolescents with marginal zone lymphoma have an excellent prognosis with limited chemotherapy or a watch-and-wait strategy after complete resection.

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Brief Report

Children and adolescents with marginal zone lymphoma have an excellent prognosis with limited chemotherapy or a watch-and-wait strategy after complete resection only

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Abbreviations:

MZL: marginal zone lymphoma

pMZL: pediatric marginal zone lymphoma

NMZL: nodal marginal zone lymphoma

EMZL: extranodal marginal zone lymphoma

SMZL: splenic marginal zone lymphoma

WHO: World Health Organisation

i-BFM: international Berlin-Frankfurt-Münster Study Group

EICNHL: European Intergroup for Childhood NHL

NHL: non-Hodgkin's lymphoma

LDH: lactate dehydrogenase

EFS: event-free survival

OS: overall survival

Abstract

Data on management of pediatric marginal zone lymphoma (MZL) are scarce. This retrospective study assessed characteristics and outcome in 66 patients <18-years-old. Forty-four (67%) had an extra-nodal (EMZL), 21 (32%) a nodal (NMZL) and one patient a splenic MZL. Thirty-three patients (50%) received a variable combination of adjuvant chemo-/immuno-/radiotherapy, whilst the remainder, including 20/21 with NMZL, entered an active observation period. Overall survival was excellent (98%±2%), although 11 patients relapsed (17%; NMZL, n=1; EMZL, n=10), 7 after any therapy, 4 after complete resection only. Conclusively, outcome of, in particular, NMZL seems to be excellent after (in)complete resection and observation only.

Introduction

Marginal zone lymphoma (MZL) is a mature B-cell lymphoma and represents a distinct clinico-pathological entity of non-Hodgkin's lymphoma (NHL). While MZL accounts for 5–17% of NHL in adulthood, it rarely occurs in children and adolescents (<2%).[1] The World Health Organisation (WHO) classification recognizes three sub-entities, including nodal MZL (NMZL), extra-nodal MZL (EMZL) and splenic MZL (SMZL).[2] As therapy guidelines for pediatric MZL (pMZL) have not yet been defined, treatment for both localized and disseminated disease varies a lot.[3-5] To get more information about clinical presentation, treatment and outcome, two of the largest consortia in childhood NHL, the international Berlin-Frankfurt-Münster (i-BFM) Study Group and the European Intergroup for Childhood NHL (EICNHL) designed a retrospective multi-national study on this rare B-cell NHL. Herein we report on 66 patients included in this study.

Results

Between May 2015 and July 2016, we performed an international survey of pMZL including only patients with nationally centrally reviewed histopathology from 16 EICNHL and/or i-BFM Study Group members. Questionnaires were sent out to obtain data on demographics and disease (age, gender, stage according to the St. Jude staging system, localisation, pre-therapeutic level of serum lactate dehydrogenase (LDH), pre-existing diseases, Helicobacter pylori-infection), treatment (surgery, chemotherapy, immunotherapy, radiotherapy, antibiotics), and outcome (remission status, relapse, death, follow-up). A total of 66 patients up to 18-years-old were identified by the national NHL study centres of the respective countries including patients diagnosed with pMZL between January 1998 and July 2016. The diagnosis was based on the WHO criteria.[2,6] Staging procedures as well as therapy protocols (Table 1) applied are described in detail elsewhere.[7-11] Patients were included in national studies or registries and treated with informed consent from the legal

guardians. Studies were conducted in accordance with the Declaration of Helsinki and approval was delivered by the ethics committees. Event-free (EFS) and overall survival (OS) were estimated with Kaplan-Meier curves.

Of the 66 patients, 21 (32%) had an NMZL, 44 (67%) an EMZL and one patient (1%) an SMZL. Median age was 14.2 years. The male-to-female ratio was 2:1. Twelve patients (18%), all of them with EMZL, had a pre-existing disorder including Sjögren's syndrome (n=2), a common variable immunodeficiency (n=2), a primary immunodeficiency not further specified (n=3), STK4 deficiency (n=1), Crigler-Najjar-syndrome (n=1), Hodgkin's lymphoma (n=1), squamous papilloma (n=1), and hyperandrogenism not further specified with hirsutism (n=1).

After a median follow-up of 2.7 years (range 0.2–12.2 years), the 5-year EFS and OS of these 66 pMZL patients were 70%±9% and 98%±2%, respectively (Figure 1-A/B). Patient's disease course is shown in Supplementary Figure S1.

Nodal marginal zone lymphoma

Among the 21 NMZL patients (Supplementary Table S1), only one was female. Median age was 14.7 years. None of them had LDH levels ≥500 U/l. All but two patients had involvement of the lymph nodes in the head-and-neck region. Eighteen (86%) had stage I, 2 (10%) stage III and in 1 patient (4%) stage of disease was not available. Seventeen (81%) had a complete resection, received no therapy and underwent a watch-and-wait strategy (Table 1). Another 3 of 4 patients underwent a watch-and-wait strategy (incomplete resection, n=2; resection status unclear, n=1). The remaining patient received systemic therapy.

One patient relapsed after 0.3 years in a distant lymph node, had another complete resection and has been in continuous complete remission for 3.9 years. Five-year EFS and OS were 94±6% and 100%, respectively (Figure 1-C/D).

Extra-nodal marginal zone lymphoma

Among the 44 EMZL patients (Supplementary Table S1), 25 (57%) were male. Median age was 13.2 years. Of the 36 patients with available LDH levels, only one had a value ≥500 U/l. Sites of involvement were: ear-nose-throat (n=16), skin (n=9), digestive tract (n=8), lungs (n=4), spleen (n=3), bone marrow (n=2), conjunctiva (n=2) and one case each, albeit not further specified, of central nervous system, orbita, breast, kidney, mediastinum and head-and-neck region. In 11 patients (25%) >1 localisation was involved, including 9 with lymph node involvement. Fifteen (34%) had stage I, 12 (27%) stage II, 12 (27%) stage III, and 3 (7%) stage IV disease. Two (5%) had no stage available. Of the 8 patients having a disease confined to the digestive tract, 2 were positive for Helicobacter pylori, 1 was negative, and for 5 patients no information was available.

Twenty-one (48%) received chemotherapy, 15 (34%) rituximab (4/15 without chemo- or radiotherapy) and 6 patients (14%) radiotherapy (5/6 without chemotherapy or rituximab) (Table 1). Three (7%) underwent allogeneic stem cell transplantation with 2 of them having an underlying immunodeficiency as indication. Nine of 20 patients (45%) with a complete resection received no therapy and underwent a watch-and-wait strategy. Another 3 of 24 patients (13%) underwent a watch-and-wait strategy (incomplete resection, n=2; resection status unclear, n=1).

Ten patients (23%) relapsed (Supplementary Table S2) after a median time of 2.1 years (range 0.7–4.8 years). First-line treatment included chemotherapy (n=2), rituximab and chemotherapy (n=1), radiotherapy (n=4), and watch-and-wait strategy (n=3). Of the three patients who relapsed after chemotherapy, all had a pre-existing disorder. Six/10 relapsed locally at the same site, 4/10 relapsed at new sites. One of the 10 relapses received a complete resection of recurrent disease and has been in continuous complete remission for 6.8 years.

Overall, 2 patients (5%) died, both having an underlying immunodeficiency, both dying from transplant-associated toxicity, 1 in first remission and 1 after relapse. Five-year EFS and OS were 64%±11% and 97±3%, respectively (Figure 1-C/D).

Splenic marginal zone lymphoma

One 17.9-years-old female patient with SMZL was treated by splenectomy only and has been in continuous complete remission for 5.2 years (Table 1, Supplementary Table S1).

Discussion

To our knowledge, this report including 66 patients with centrally reviewed pMZL represents by far the largest series of pMZL in childhood and adolescence reported to date. Due to its rarity, only few case reports and series have been published so far.[4,5,12]

Our results show that pMZL is associated with male gender, older age, localized stage I/II disease, low pre-therapeutic LDH levels and a higher proportion of the EMZL subtype. Nevertheless, as we also identified stage IV patients, exclusively in EMZL, initial diagnostic work-up should always follow the modified St. Jude Staging System.[13] Almost all our NMZL patients presented with isolated involvement of head-and-neck lymph nodes. In 81% of them a complete resection was feasible followed by a watch-and-wait strategy and resulting in an excellent prognosis with only one relapse. In contrast, 73% of our EMZL patients were treated by systemic chemo-/immuno-/radiotherapy. Interestingly, they had a high relapse rate, despite two-thirds of the relapsed cases receiving up-front chemo-/radiotherapy. Salvage therapy was successful in almost all relapsed EMZL cases resulting in a 5-year OS of 97%±3%.

Taking our results into account, the indication for intense chemo-/immuno-/radiotherapy should be re-considered to avoid unnecessary short- and long-term toxicity in pMZL.[14,15] Similar strategies as for pediatric follicular lymphoma and early-stage nodular

lymphocyte-predominant Hodgkin's lymphoma should also be pursued in pMZL.[16,17] A complete resection without the risk of mutilation followed by observation may not only be justified in localised NMZL, but perhaps also in case of incomplete resection of stage I/II disease (2 of our patients) or localized relapse (1 patient).[4,5] Although our study could not support the use of antibiotics in case of a proven infection, they could be tried in addition or even up-front.[18] In view of the good overall survival in advanced EMZL (all but 2 of our 15 stage III/IV patients are alive), low-intensity chemotherapy±rituximab could be an option whereas conventional chemotherapy±rituximab may instead be reserved for disseminated relapse or progression, as the majority of the B-NHL protocols still include anthracyclines, alkylating agents and intrathecals.[10,19]

There are several limitations when analysing data from a multi-national retrospective survey on a very rare lymphoma subtype, all of which necessitate further evaluation in well-defined prospective trials. As such, we were unable to report on genetic studies, infectious status and, in particular, on how and why the decisions were taken by the responsible physicians to follow a watch-and-wait strategy in (in)completely resected disease.[12]

Conclusively, regardless of the therapy the patients received, it seems that pMZL does not automatically require chemotherapy due to the excellent outcome in at least localised NMZL.[4,5] For more disseminated and relapsed cases, future clinical trials are necessary to establish the best therapy with the lowest amount of toxicity.

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Group (CCLG), Nordic Society of Pediatric Hematology and Oncology (NOPHO), Belgian Society of Pediatric Hematology and Oncology (BSPHO), Dutch Childhood Oncology Group (DCOG), Israel's Society of Pediatric Hematology and Oncology, Slovenian Society of Hematology and Oncology, Serbian Society of Hematology and Oncology, Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), Hong Kong Pediatric Hematology and Oncology Study Group (HKPHOSG) and a single institution from Canada (Toronto).

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Legends

Figure 1: 5-year event-free and overall survival of the 66 patients with pediatric marginal zone lymphoma (pMZL; A, B) and of the 21 patients with nodal marginal zone lymphoma *vs.* the 44 patients with extra-nodal marginal zone lymphoma (NMZL *vs.* EMZL; C, D)

295 **Authorship contributions**

296 AA, OA, and BB designed and planned the study; AA and LR wrote the manuscript;
297 AA and LR were in charge of data pooling, data checking and statistical analysis; all other
298 authors (SBB, SB, LB, AC, JJ, EK, JL, AB, GM, KM, FN, FT, TO, MP, CD, MG, OM, DW,
299 and WW) as well as AA, OA and BB were principal or co-investigators in their study groups
300 and institutions, coordinated the national trials in their countries, provided study materials
301 and recruited patients. All authors read and approved the final version of the manuscript.

302

303 **Conflict-of-interest disclosure:** The authors declare no competing financial interests.

Table 1. Treatment characteristics as well as outcome of patients with pMZL, NMZL, EMZL, and SMZL

	pMZL		NMZL		EMZL		SMZL
	No. of pts.	%	No. of pts.	%	No. of pts.	%	No. of pts.
Variable	66		21		44		1
Treatment							
chemotherapy § π	22	33	1	5	21	48	0
alone	10		0		10		
with rituximab	12		1		11		
with radiotherapy	1		0		1		
rituximab §	16	24	1	5	15	34	0
alone	4		0		4		
with chemotherapy	12		1		11		
with radiotherapy	1		0		1		
radiotherapy §	6	9	0		6	14	0
alone	5				5		
with chemotherapy	1				1		
with rituximab	1				1		
watch-and-wait	33	50	20	95	12	27	1
Complete resection	38	58	17	81	20	45	1
watch-and-wait	27		17		9		1
Incomplete resection	26	39	3	14	23	52	0
watch-and-wait ~	4		2		2		0
Resection status n. a.	2	3	1	5	1	2	0
watch-and-wait	2		1		1		0
Antibiotics							
yes	8	12	1	5	7	16	0
no	58	88	20	95	37	84	1
Allo-SCT in 1st CR							
yes	3	5	0		3	7	/
no	63	95	21	100	41	93	1
Outcome							
1st CCR	54	82	20	95	33	75	1
relapse	11	17	1	5	10	23	0
death as 1st event Ω	1	2	0		1	2	0
5-year EFS	70±9%		94±6%		64±11%		100%
5-year OS	98±2%		100%		97±3%		100%

Follow-up (y)				
median	2,7	2,2	3,2	5,2
range	0,2-12,2	0,2-4,4	0,2-12,2	/

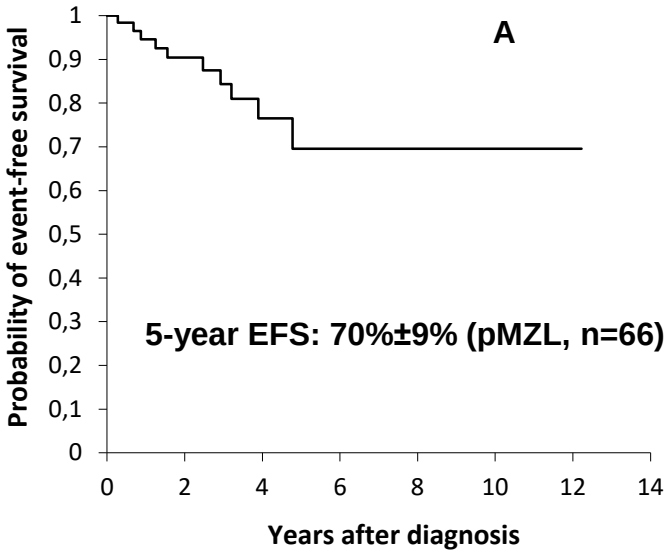
Abbreviations: pMZL, pediatric marginal zone lymphoma; NMZL, nodal MZL; EMZL, extra-nodal MZL; SMZL, splenic MZL; No. of pts., number of patients; y, years; n. a., not available; allo-SCT, allogeneic stem cell transplantation; CR, complete remission; CCR, complete continuous remission; EFS, event-free survival; OS, overall survival

§ 1 patient with EMZL received chemotherapy + rituximab + radiotherapy.

Π according to NHL-BFM (n=11), LMB (n=3), and JACLS (n=1) protocols; CHOP (n=3), CVP (n=1), miscellaneous regimens (n=3).

~ All 4 patients with incomplete initial resection and watch-and-wait are in remission.

Ω Patient died from transplant-related toxicity.


A
Probability of event-free survival
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
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2
4
6
8
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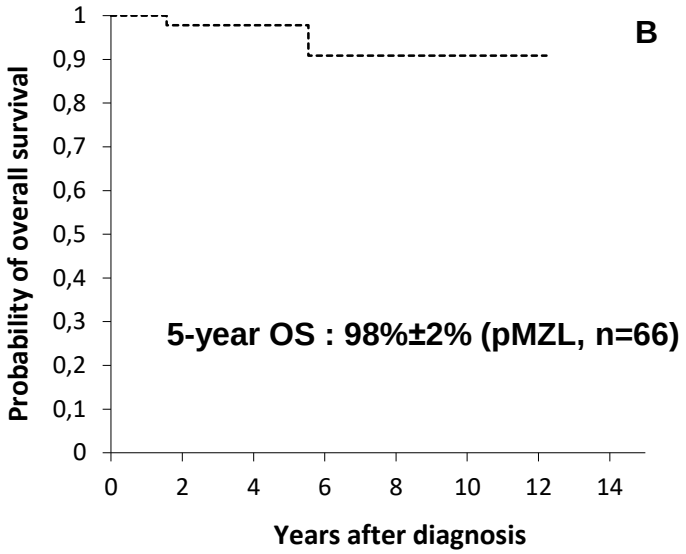
12
14
Years after diagnosis
5-year EFS: 70%±9% (pMZL, n=66)


B
Probability of overall survival
1
0,9
0,8
0,7
0,6
0,5
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0,1
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6
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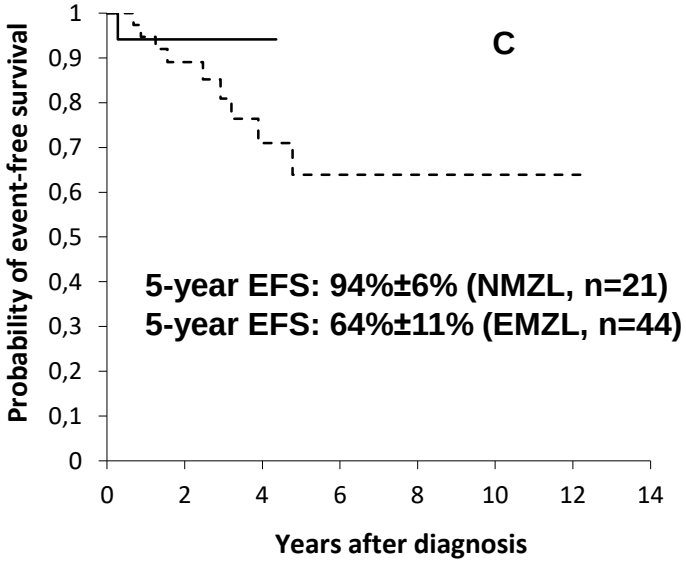
12
14
Years after diagnosis
5-year OS : 98%±2% (pMZL, n=66)


C
Probability of event-free survival
1
0,9
0,8
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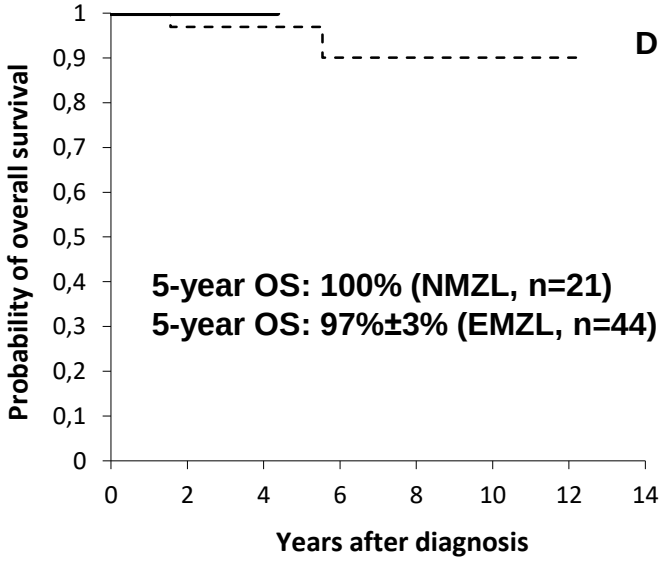
Years after diagnosis
5-year EFS: 94%±6% (NMZL, n=21)
5-year EFS: 64%±11% (EMZL, n=44)


D
Probability of overall survival
1
0,9
0,8
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6
8
10
12
14
Years after diagnosis
5-year OS: 100% (NMZL, n=21)
5-year OS: 97%±3% (EMZL, n=44)

Supplemental Table S1. Clinical and laboratory characteristics of patients with pMZL, NMZL, EMZL, and SMZL

	pMZL		NMZL		EMZL		SMZL
	No. of pts.	%	No. of pts.	%	No. of pts.	%	No. of pts.
Variable	66		21		44		1
Gender							
male	45	68	20	95	25	57	/
female	21	32	1	5	19	43	1
Age (y)							
median	14,2		14,7		13,2		/
range	2,2-17,9		2,2-17,8		4,3-17,5		17,9
<10	9	14	3	14	6	14	/
≥10 - 15	36	54	10	48	26	59	/
≥15 - 18	21	32	8	38	12	27	1
Pre-existing disorder							
present	12	18	0		12	27	/
absent	54	82	21	100	32	73	1
sLDH level (U/l)							
median	216		190		249		/
range	129-529		129-411		133-529		/
<500	53	80	17	81	35	80	1
≥500	1	2	0		1	2	/
n. a.	12	18	4	19	8	18	/
Stage of disease							
stage I	33	50	18	86	15	34	/
stage II	12	18	0		12	27	/
stage III	14	21	2	9	12	27	/
stage IV	4	6	0		3	7	1*
n. a.	3	5	1	5	2	5	/
Histopathology							
NMZL	21	32	21	100	/		/
EMZL	44	67	/		44	100	/
SMZL	1	1	/		/		1
Sites of involvement #							
lymph nodes	30	45	21	100	9	20	0
ear-nose-throat	16	24	0		16	36	0
skin	9	14	0		9	20	0

digestive tract	8	12	0	8	18	0
lungs	4	6	0	4	9	0
spleen	4	6	0	3	7	1
conjunctiva	2	3	0	2	5	0
bone marrow	3	5	0	2	5	1*
other ∑	6	9	0	6	14	0

Abbreviations: pMZL, pediatric marginal zone lymphoma; NMZL, nodal MZL; EMZL, extra-nodal MZL; SMZL, splenic MZL; No. of pts., number of patients; y, years; sLDH, serum lactate dehydrogenase; n. a., not available

11 patients with EMZL and 1 patient with SMZL had >1 site of involvement.

∑ Central nervous system (n=1), head-and-neck not further specified (n=1), mediastinum (n=1), kidneys (n=1), orbita not further specified (n=1), breast (n=1).

* Bone marrow involvement was questionable.

Supplemental Table S2. Clinical, laboratory and treatment characteristics as well as outcome of the 11 patients with relapsed pMZL

	relapsed MZL No. of pts.	%
Variable	11	
Gender		
male	6	55
female	5	45
Age (y)		
median	14,7	
range	6,8-17,3	
<10	1	9
≥10 - 15	6	55
≥15 - 18	4	36
Pre-existing disorder		
present $	4	36
absent	7	64
sLDH level (U/l)		
median	267	
range	138-431	
<500	9	82
n. a.	2	18
Stage of primary disease		
stage I	5	45
stage II	2	18
stage III	3	27
stage IV	1	9
Histopathology		
NMZL	1	9
EMZL	10	91
Sites of primary involvement		
lymph nodes	1	9
ear-nose-throat	5	45
skin	4	36
central nervous system	1	9
First-line treatment		

chemotherapy	3	27
alone	2	
with rituximab	1	
rituximab	1	9
alone	0	
with chemotherapy	1	
radiotherapy	4	27
alone	4	
Complete initial resection	10	91
watch-and-wait	4	
Incomplete initial resection	1	9
watch-and-wait	0	
Initial antibiotics		
yes	0	
no	11	100
Allo-SCT in 1st CR		
yes	1	9
no	10	91
Sites of involvement at relapse #		
lymph nodes	4	36
ear-nose-throat	3	27
skin	4	36
central nervous system	1	9
Therapy of relapse		
chemotherapy	4	36
alone	1	
with rituximab	3	
rituximab *	6	55
alone	2	
with chemotherapy	3	
with radiotherapy	1	
radiotherapy	3	27
alone	2	
with rituximab	1	
watch-and-wait §	2	18
Allo-SCT for relapse	1	9
Outcome		
2nd CCR	10	91
death Ω	1	9

Follow-up (y)	
median	6,1
range	0,8-12,2

Abbreviations: pMZL, pediatric marginal zone lymphoma; NMZL, nodal MZL; EMZL, extra-nodal MZL; No. of pts., number of patients; y, years; sLDH, serum lactate dehydrogenase; n. a., not available; allo-SCT, allogeneic stem cell transplantation; CR, complete remission; CCR, complete continuous remission

$ Sjögren's syndrome (n=1), primary immunodeficiency not further specified (n=2), Crigler-Najjar-syndrome (n=1).

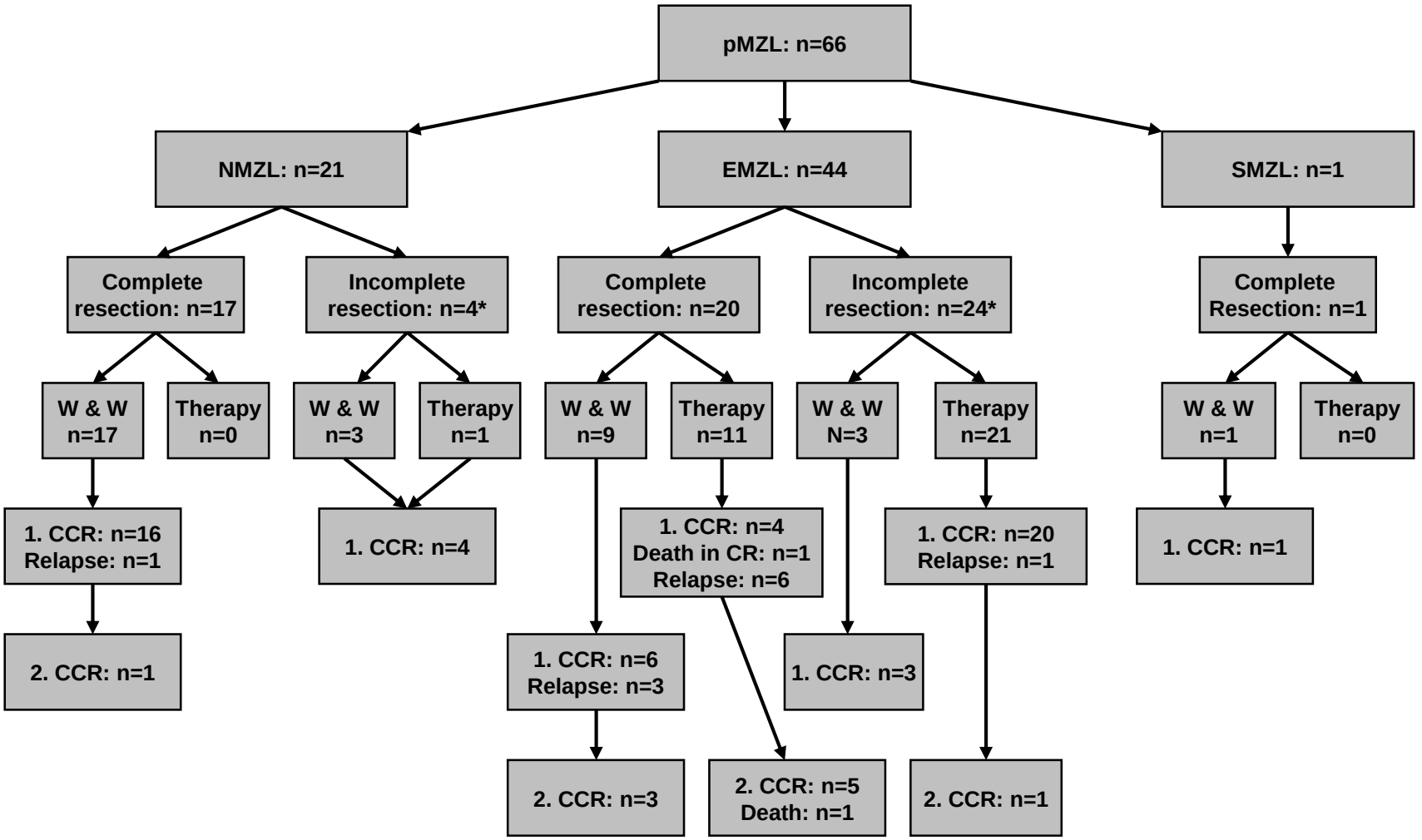
1 patient with EMZL had >1 site of involvement.

* 1 of the 6 patients received intralesional rituximab only.

§ Both patients had a complete resection of their disease.

Ω Patient died from transplant-related toxicity.

Supplemental figure S1: Flow chart for the disease course of the 66 patients with pMZL



Abbreviations: MZL, marginal zone lymphoma; pMZL, pediatric MZL; NMZL, nodal MZL; EMZL, extranodal MZL; SMZL, splenic MZL; W & W, watch-and-wait; CCR, continuous complete remission; CR, complete remission

*including 1 patient with an unclear resection status